## REMARKS

Upon entry of the amendment, claims 1, 3-9, and 11-19, and 21 will be pending in the application. Claims 2 and 20 have been cancelled and new claim 21 added. Claims 1, 4, 9, 10, 14, 18, and 19 have been amended. Support for the amendmentbs appears in, e.g., page 7, lines 16-21 (describing conditional attachment or removal of separation elements based on the nature of a distinguishing element), in page 5, lines 3-5 (describing separation of nucleic acid sequences not containing the attached separation group from complexes containing the attached separation group), and in the claims as filed. An appendix showing claim amendment is attached.

A sequence listing accompanies this response. No new matter has been added.

**Rejections under 35 USC 112, second paragraph**

Claims 1-20 are rejected as indefinite, on various grounds. The rejection is traversed to the extent it is applied to the claims as amended.

Claims 1-17 are rejected as indefinite for reciting the phrase "thereby forming an immobilized targeting element-separation group complex", apparently on the basis that it is unclear whether the nucleic acid of interest is a component of the complex (see paragraph 2a of the Office Action). Claim 1, from which the remaining claims subject to the rejection depend, has been amended to specify that the complex includes the nucleic acid of interest.

Claims 6-12 are rejected as indefinite on the basis that the phrase "said oligonucleotide" in claim 6 lacks antecedent basis. (Paragraph 2b of the Office Action). This aspect of the rejection is respectfully traversed. Basis for "oligonucleotide" in claim 6 appears in claim 5, from which claim 6 directly depends.

Claims 10-12 are rejected as indefinite on the basis that claim 10, from which the remaining claims subject to the rejection depend, does not further limit the claim from which claim 10 depends (Paragraph 2c of the Office Action). Claim 10 has been amended to depend from claim 3.

Claim 18 is rejected as indefinite for reciting the phrase "thereby forming a second immobilized targeting element-separation group complex," on the basis that is unclear whether the nucleic acid of interest is a component of the complex (paragraph 2d of the Office Action). Claim 18 has been amended to specify that the complex includes the nucleic acid of interest.

Claim 18 is additionally rejected as indefinite, on the basis that it is unclear at what point in the method of claim 1 the further method steps are performed. (Paragraph 2f of the Office Action) Claim 18 has been amended to further specify that the second targeting element contacts the population of nucleic acid molecules simultaneously with the first targeting element.

Claim 19 has been rejected as indefinite for omitting essential steps. Claim 19 has been amended to specify that the method includes in step (e) removing the immobilized targeting group complex comprising said nucleic acid of interest from nucleic acid sequences not containing the attached separation group.

In view of the foregoing comments, reconsideration and withdrawal of the rejections for indefiniteness is requested.

**Rejections under 35 USC 102**

Claims 1-6, 13, 17, 19 and 20 are rejected as anticipated by Rigas et al., Proc. Nat. Acad. Sci. USA 83:9591-95, 1986 ("Rigas"). The rejection is traversed to the extent it is applied to the claims as amended. Claim 1, from which depends claims 2-6, 128, and 17, has been amended so

that the method requires selectively attachment a separation group to the bound targeting element, and that attachment of the separation group is dependent on the nature of a distinguishing element.

Rigas does not describe selective attachment of a separation group as required by the claims. The attachment of a separation group (streptavidin) to a targeting element (biotinylated probe, which includes a sequence-specific distinguishing element) as described therein is not based on the nature of the distinguishing element: It occurs to all biotinylated probes, regardless of whether they are hybridized to a targeted fragment or not (see p. 9591, right column, lines 1-10 from bottom: "Avidin is added to the reaction solution to bind the biotinylated probe, both free and complexed with plasmid"). Thus, this process represents a single discriminatory step that is limited in specificity by the differential in hybridization between fully and partially complementary sequences; it can give rise to considerable background due to non-specific binding of potentially numerous partially matched sequences to the extraction probe, in particular of sequences containing a few or single mismatches.

In contrast, the selective attachment of the separation group as required by the claims provides a level of sequence-dependent selection, considerably beyond the specificity of hybridization alone. It results in an additional, highly specific selection mechanism that cannot be achieved in conventional one-step binding assays such as hybridization-based capture of nucleic acids as described by Rigas.

Claim19 has been amended to require in step (c) selectively removing the attached separation group from the bound targeting element, wherein removal of the separation group is dependent on the nature of the distinguishing element. As is discussed above, Rigas does not describe a method that includes this selective attachment step.

Claims 1-8, 13, 15 and 17-20 are rejected as anticipated by Tyagi et al., US Patent No. 5,759,773 ("Tyagi"). The rejection is traversed to the extent it is applied to the claims as amended.

As is discussed above, claim 1, from which depends claims 2-7, 13, 15, and 17, has been amended to specify that the method requires selectively attaching a separation group to the bound targeting element, and that the selective attachment of the separation group is dependent on the nature of a distinguishing element. Claim 19 analogously requires in step (c) selectively removing the attached separation group from the bound targeting element, wherein removal of the separation group is dependent on the nature of the distinguishing element.

Tyagi describes nucleic acid sandwich hybridization assays that incorporate one or a combination of background reduction steps. Those steps include use of a separate capture probe and separation from immobilized capture probes by cleavage and isolation (see Abstract). The capture of the hybridized complex in Tyagi is based on the nature of the capture probe alone, while the reporter probe is used for signal generation (column 12, lines 12-15). The detection sensitivity achieved by Tyagi relies on capture probe and reporter probe being separate. The two probes are - and remain - two separate oligonucleotides that anneal to different regions of the targeted fragment, and the separation group (biotin as part of the capture probe) does not get attached to targeting element (reporter probe) other than indirectly through hybridization to the same targeted fragment (see column 12, line 42: capture probes are separate from reporter probes and do not get modified in the course of the assay). Immobilization is performed only for the purpose of washing off unbound reporter probes in order to reduce background due to target-independent ligation, but not to achieve separation of the targeted nucleic acid itself. Thus, the separation group does not get attached based on the nature of the distinguishing element, since it

is part of the reporter probe - in other words, the selectivity of capture / extraction is not enhanced or affected in any way by the identity of the distinguishing element. Thus, Tyagi does not describe or suggest a method that includes the required step of selectively attaching a separation group to the bound targeting element.

In view of the foregoing comments, reconsideration and with withdrawal of the rejections for anticipation is requested.

Rejections under 35 USC 103

Claims 9-12, 14, and 16 are rejected as obvious over Tyagi in view of Edman et al., US Patent No. 6,309,833 ("Edman").[a] The rejection is traversed to the extent it is applied to the claims as amended.

Claims 9-12 have been amended to depend from claims not subject to this rejection. Claims 14 and 16 depend from claim 1, which has been amended to require selectively attaching a separation group to the bound targeting element. Tyagi, as is explained above, lacks any suggestion of this feature of the claimed invention.

Edman describes a method for amplifying nucleic acids wherein detection of amplified species is enhanced by the use of asymmetric amplification. The reference explains that amplification is made asymmetric by using divergent ratios of amplification primers or by using non-extending and/or non-cleavable amplification primers. Detection of the amplicons is improved because maintenance of single stranded species of amplicons during amplification facilitates their direct capture by immobilized probes without having to include denaturing steps (see Abstract).

However, Edman fails to describe or suggest selectively attaching a separation group to the bound targeting element, which is required the claimed invention. Accordingly, claim 1 is non-obvious in view of the cited references. Claims 14 and 16 are therefore also non-obvious over the cited references.

In view of the foregoing comments, reconsideration and with withdrawal of the rejections for obviousness is requested.

Double-patenting Rejections

Claims 1-18 are rejected for statutory-type double patenting in view of claims 1-18 of copending application USSN 09/733,846 ("the '846 application"). Claims 19 and 20 are rejected for obviousness-type double-patenting in view of the '846 application.

Applicants will address the double-patenting rejections upon indication of otherwise allowable subject matter.

**CONCLUSION**

[a] Applicants note this rejection is listed as a rejection under 35 USC 102(b) in the Office Action. Applicants believe the intended rejection was for obviousness under 35 USC 103(a).

Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

A petition for extension of time accompanies this submission. The Commissioner is hereby authorized to charge payment of any additional fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 22650-001CIP).

Respectfully submitted,

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## Appendix

In the claims:

Cancel claims 2 and 20.

Amend the following claims:

1. (Amended) A method for separating a nucleic acid of interest from a population of nucleic acid molecules, the method comprising;

providing a population of nucleic acid molecules comprising at least one nucleic acid sequence of interest, wherein said at least one nucleic acid sequence of interest includes a distinguishing element;

contacting said population of nucleic acid molecules with a first targeting element, wherein said first targeting element binds specifically to at least one nucleic acid sequence of interest in said population of nucleic acid molecules;

selectively attaching a separation group to said bound targeting element, wherein attachment of said separation group is dependent on the nature of said distinguishing element;

immobilizing said attached separation group to a substrate, thereby forming an immobilized targeting element-separation group complex comprising said at least one nucleic acid sequence of interest; and

removing said immobilized targeting element-separation group complex comprising said at least one nucleic acid sequence of interest from said population of nucleic acid molecules, thereby separating said nucleic acid sequence of interest from said population of nucleic acid molecules.

3. (Amended) The method of claim [2] 1, wherein said targeting element binds to said at least one nucleic acid sequence of interest at a sequence within 20 nucleotides of said distinguishing element.

4. (Amended) The method of claim [2] 1, wherein said targeting element comprises a nucleic acid sequence.

5. The method of claim 4, wherein said targeting element is an oligonucleotide.

6. The method of claim 5, wherein said oligonucleotide has an extendable 3‘ hydroxy terminus.

7. The method of claim 6, wherein said separation group is an immobilizable nucleotide.

8. The method of claim 7, wherein said immobilizable nucleotide is a biotinylated nucleotide.

9. (Amended) The method of claim [6] 8, wherein said separation group is attached to said targeting element by extending said oligonucleotide with a polymerase in the presence of said biotinylated nucleotide, thereby forming an extended oligonucleotide primer containing said immobilizable nucleotide.

10. (Amended) The method of claim [9] 3, wherein said targeting element is an oligonucleotide.

11. The method of claim 10, wherein said separation group is an immoblizable nucleotide.

12. The method of claim 11, wherein said immobilizable nucleotide is a biotinylated nucleotide.

13. The method of claim 1, wherein said population of nucleic acids is a population of DNA molecules.

14. (Amended)The method of claim 13, wherein said population of DNA molecules is a population of [genomic DNA molecules or a population of] cDNA molecules.

15. The method of claim 1, wherein said population of nucleic acid molecules is a population of RNA molecules.

16. (Amended) The method of claim [2] 1, wherein said distinguishing element is a single nucleotide polymorphism.

17. The method of claim 1, wherein said substrate is a particle, bead, magnetic bead, or glass surface.

18. (Amended) The method of claim 1, further comprising

contacting said population of nucleic acid molecules with a second targeting element simultaneously with said first targeting element, wherein said second targeting element

binds specifically to a second at least one nucleic acid sequence of interest in said population of nucleic acid molecules;

attaching a second separation group to said second bound targeting element;

immobilizing said attached second separation group to a substrate, thereby forming a second immobilized targeting element-separation group complexcomprising said second at least one nucleic acid sequence of interest; and

removing said immobilized targeting element-separation group complex comprising said second at least one nucleic acid sequence of interest from said population of nucleic acid molecules, thereby separating said second at least one nucleic acid sequence of interest from said population of nucleic acid molecules.

19. (Amended) A method for separating a nucleic acid of interest from a population of nucleic acid molecules, the method comprising;

(a) providing a population of nucleic acid molecules comprising at least one nucleic acid sequence of interest, wherein said at least one nucleic acid sequence of interest includes a distinguishing element;

(b) contacting said population of nucleic acid molecules with a targeting element attached to a separation group, wherein said population of nucleic acid molecules comprises a targeting element which binds specifically to at least one nucleic acid sequence of interest in said population of nucleic acid molecules;

(c) selectively removing said attached separation group from said bound targeting element, wherein removal of said separation group is dependent on the nature of said distinguishing element;

(d) immobilizing to a substrate separation groups remaining [said] attached [separation group to a substrate] to said targeting element, [therby] thereby forming an immobilized targeting element-separation group complex; and

(e) removing said immobilized targeting group complex [from nucleic acid sequence of interest] comprising said nucleic acid of interest from nucleic acid sequences not containing the attached separation group,

thereby separating said nucleic acid sequence of interest from said population of nucleic acid molecules.

Add the following new claim:

21. (New) The method of claim 13, wherein said population of DNA molecules is a population of genomic DNA molecules.